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Infections Present on Admission Compared with Hospital-Acquired Infections in Acute Ischemic Stroke Patients

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Abstract

Background—To date, few studies have assessed the influence of infections present on admission (POA) compared with hospital-acquired infections (HAIs) on neurologic deterioration (ND) and other outcome measures in acute ischemic stroke (AIS).

Methods—Patients admitted with AIS to our stroke center (July 2010 to December 2010) were retrospectively assessed. The following infections were assessed: urinary tract infection, pneumonia, and bacteremia. Additional chart review was performed to determine whether the infection was POA or HAI. We assessed the relationship between infections in ischemic stroke

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patients and several outcome measures including ND and poor functional outcome. A mediation analysis was performed to assess the indirect effects of HAI, ND, and poor functional outcome.

Results—Of the 334 patients included in this study, 77 had any type of infection (23 POA). After adjusting for age, National Institutes of Health Stroke Scale at baseline, glucose on admission, and intravenous tissue plasminogen activator, HAI remained a significant predictor of ND (odds ratio [OR] = 8.8, 95% confidence interval [CI]: 4.2–18.7, $P < .0001$) and poor functional outcome (OR = 41.7, 95% CI: 5.2–337.9, $P = .005$), whereas infections POA were no longer associated with ND or poor functional outcome. In an adjusted analysis, we found that 57% of the effect from HAI infections on poor functional outcome is because of mediation through ND ($P < .0001$).

Conclusions—Our data suggests that HAI in AIS patients increases the odds of experiencing ND and subsequently increases the odds of being discharged with significant disability. This mediated effect suggests a preventable cause of ND that can thereby decrease the odds of poor functional outcomes after an AIS.

Keywords

Infection; ischemic stroke; outcomes research; acute cerebral infarction; health policy; stroke treatment

Introduction

Up to one third of patients with acute ischemic stroke (AIS) will clinically deteriorate during the first few days after hospital admission.^{1–4} Although this process may be reversible depending on the etiology of deterioration, it places patients at higher risk of poor functional outcome and mortality.^{3–7} One such etiology of neurologic deterioration (ND) is infection, either present on admission (POA) or hospital-acquired infections (HAIs).

HAIs are the most common complication of hospitalized patients and a leading complication among patients with stroke.^{8,9} HAIs impose a significant burden on the US health-care system, accounting for 99,000 deaths and \$28–\$45 billion dollars in direct costs to hospitals annually.^{10,11} Infection of any kind, occurring at any time point, has been shown to increase length of stay, worsen functional outcome, and increase mortality.¹² The mechanism is thought to be mediated by systemic inflammation after stroke,¹³ which contributes to fever, delirium,^{14,15} worsening neurologic function,¹⁶ mental status changes, and risk of multiorgan dysfunction or death.⁹ Elevations in peripheral leukocyte levels, independent of an underlying infectious process, are also thought to increase the risk of ND and result in poor functional outcome.^{16–18}

Prior research has focused on infections after patients have been admitted with a stroke, but no study has assessed whether a difference in outcomes exists for stroke patients with an infection POA versus a HAI.¹⁹ We investigated the association between infection and ND and other adverse outcomes in AIS patients. Furthermore, we investigated whether HAIs or infections POA had different impacts on the odds of ND or outcomes poststroke.

Methods

Study Population and Variable Definition

We conducted a single-center retrospective analysis of a prospectively collected stroke registry, for patients admitted with AIS from July 2008 to December 2010. Patients who experienced an in-hospital stroke, were transferred from another facility, had an unknown time of last seen normal, presented more than 48 hours after last seen normal, or had incomplete data were excluded. Infections were defined as follows: urinary tract infection (UTI) if more than 100,000 colony forming units per milliliter of known microbial species were detected on urine culture or pyuria (>5 WBC/HPF) and bacteriuria, pneumonia (PNA), defined as a positive chest x-ray in the presence of clinical findings suggestive of PNA,²⁰ and bacteremia if more than 10,000 colony forming units are present in a venous blood sample and there was no evidence of obvious contaminants. Obvious contaminants were classified as coagulase-negative *Staphylococcus*, diphtheroids, *Micrococcus* spp., *Bacillus* spp., and viridans group streptococci if only 1 of 2 blood cultures was positive. Urinalysis is ordered for all patients as part of a standardized order set. A culture would be performed in the presence of a urinalysis suggestive of infection or with clinical symptoms or signs. Additional chart review was performed to determine whether the infection was POA or HAI. Infection POA was defined as any infection being diagnosed at or within the first 24 hours of admission. Any infection diagnosed 24 hours after admission was classified as a HAI. We chose 24 hours instead of 48 hours to ensure that infections POA are classified as infections that are present at the time the order for inpatient admission occurs, consistent with the Centers for Medicare and Medicaid definition. The National Healthcare Safety Network defines HAI, or nosocomial infection, as a localized or systemic condition that is preventable and results from an adverse reaction to the presence of an infectious agent, with no evidence that the infection was present or incubating at the time of admission to the acute care setting.²¹

Outcome Definition

The primary outcomes of interest were ND (previously defined as an increase in the National Institutes of Health Stroke Scale [NIHSS] score of 2 or more points in a 24-hour period during hospital stay)⁴ and poor functional independence at the time of discharge, as measured by a modified Rankin Scale (mRS) score of 3–6. Secondary outcome of interest was unfavorable discharge disposition (defined as discharge to a facility other than home or an inpatient rehabilitation center).⁴ We stratified infection status by POA or HAI to determine if there were differences in stroke outcomes for patients who are admitted with an infection compared with those who develop HAI. Furthermore, we divided infections into specific types of infection (ie, UTI, PNA, bacteremia) and then assessed their influence on functional and neurologic outcomes after stroke.

Statistical Analysis

Frequencies and percents were compared using Pearson chi-square or Fisher exact test, where appropriate. Medians were compared using the Wilcoxon rank sum test. The outcome measures were dichotomized as previously described, and logistic regression was used to assess the associations between the predictor variables on the outcomes of interest.

Mediation analysis using the Sobel test was performed to assess the complex relationships between infections, ND, and other outcome measures. Mediation occurs when (1) the independent variable significantly affects the mediator, (2) the independent variable significantly affects the dependent variable in the absence of the mediator, (3) the mediator has a significant unique effect on the dependent variable, and (4) the effect of the independent variable on the dependent variable decreases when the mediator is added to the model.^{22,23} The Sobel test (capable of handling dichotomous mediators and outcomes) was used to test whether the indirect effect of the independent variable on the dependent variable through the mediator is significantly different than zero. As this was an exploratory analysis, no adjustments were made for multiple comparisons.²⁴ All tests were performed at the alpha .05 level.

Results

Baseline Characteristics

Of the 334 patients included in the study, 77 (23.1%) were found to have either an infection POA or a HAI. Of these patients, 19 (24.4%) patients had bacteremia, 50 (64.1%) had UTI, 29 (37.2%) had PNA, and 22 (28.2%) patients had more than 1 infection. Of the 23 (29.9%) patients who had an infection POA, 12 (63.2%) were diagnosed with UTI, 1 (5.3%) had PNA, and 6 (31.6%) were diagnosed with bacteremia. Differences in baseline characteristics are shown in Table 1.

Neurologic Deterioration

HAI patients had higher percentages of ND compared with patients with POA infections and those without any infection (79.6% versus 47.8% versus 24.7%; $P < .0001$). Patients with an infection at any time (HAI or POA) are at nearly 7-fold greater odds of ND compared with patients without any infection (odds ratio [OR] = 6.86, 95% confidence interval [CI]: 3.92–11.99, $P < .0001$). Adjusting for age, NIHSS at baseline, and serum glucose on admission, infection at any time remained significantly associated with ND (OR = 4.86, 95% CI: 2.70–8.70, $P < .0001$). Infections POA were by themselves associated with ND (OR = 2.79, 95% CI: 1.18–6.64, $P = .0211$), but HAI was associated with even greater odds of ND during hospitalization (OR = 11.9, 95% CI: 5.80–24.5, $P < .0001$). Adjusting for age, NIHSS at baseline, glucose on admission, and treatment with intravenous tissue plasminogen activator (IV tPA), HAI remained significantly associated with ND (OR = 8.80, 95% CI: 4.20–18.70, $P < .0001$), whereas POA infection was no longer statistically significantly associated with ND (OR = 1.60, 95% CI: .60–4.13, $P = .3515$). Figure 1 illustrates the relationship, crude and adjusted, between any type of infection, POA infections, and HAI with ND.

Assessing the source of infection separately with ND as the outcome, UTI, PNA, and bacteremia were significant predictors of ND (Table 2). Adjusting for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA, the UTI, PNA, and bacteremia remained significant predictors of ND.

Poor Functional Outcome

The mRS score at discharge was the highest for HAI infections, followed by POA infections and lastly the no infection group (5 versus 4 versus 2; $P < .0001$). Infection at any time was significantly associated with poor functional outcome (discharge mRS score 3–6) compared with patients without any infection (OR = 9.30, 95% CI: 4.30–20.1, $P < .0001$); after adjusting for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA, infection at any time remained independently associated with poor functional outcome (OR = 4.20, 95% CI: 2.20–7.80, $P < .0001$). POA infection was associated with poor functional outcome (OR = 3.0, 95% CI: 1.10–7.9, $P = .0211$), but again HAI infections put patients at dramatically greater odds of being discharged with a mRS score of 3–6 (OR = 56.4, 95% CI: 7.70–414, $P < .0001$). After adjusting for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA, HAI infection remained significantly associated with poor functional outcome (OR = 34.4, 95% CI: 4.30–275, $P = .0009$), whereas POA infection was no longer statistically significantly associated with poor functional outcome (OR = 1.05, 95% CI: .25–4.40, $P = .9419$). Figure 1 illustrates the relationship, crude and adjusted, between any type of infection, POA infections, and HAI with poor functional outcome.

Discharge Disposition

Patients with HAI and POA infections had more unfavorable discharge dispositions than those without an infection (47.8% versus 42.6% versus 14.3%; $P < .0001$). Additionally, patients with a HAI had a longer median length of stay compared with those with infections POA and no infection (14 versus 9 versus 4; $P < .0001$). An infection at any time was associated with unfavorable discharge disposition (OR = 4.36, 95% CI: 2.62–8.19, $P < .0001$). Adjusting for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA, infection remained a statistically significant predictor of unfavorable discharge disposition (OR = 2.26, 95% CI: 1.14–4.48, $P = .0196$). An infection POA was associated with poor discharge disposition (OR = 5.50, 95% CI: 2.26–13.41, $P = .0002$), but after adjusting for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA, infection POA was no longer associated with poor discharge disposition (OR = 1.50, 95% CI: .44–5.12, $P = .5176$). HAI was associated with poor discharge disposition even after adjusting for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA (OR = 2.497, 95% CI: 1.196–5.214, $P = .0148$).

Mediation Analysis Assessing HAI, Neurologic Deterioration, and Poor Functional Outcome

To further investigate this issue, we performed a mediation analysis to assess the combined effects of infections, ND, and poor functional outcome, with infection as an independent variable, poor functional outcome as a dependent variable, and ND as a mediator. Infection occurred before ND in 15 (39.5%) of the 38 HAI patients who experienced ND. Mediation analysis using the Sobel method with standardized notation was performed only for HAI infections because the adjusted model for the POA infections predicting poor functional outcome was not significant. Adjusting for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA use, we found that 57% of the effect from HAI infections on poor functional outcome was because of mediation through ND ($P < .0001$).

Discussion

In our cohort, we found that 30% of ischemic stroke patients have an infection during their hospital stay, with 24% of these patients presenting with an infection on admission. These proportions are similar to those found in a recent meta-analysis by Westendorp et al.²⁵ Similar to prior investigations,²⁶ patients who presented at our center with an infection or developed an infection after hospitalization were more likely to be older and have presented with more severe strokes—2 factors which we have previously shown to be strongly associated with ND.³ Other factors associated with developing an infection included higher admission glucose, cortical involvement on brain imaging, and comorbidities including history of coronary artery disease, atrial fibrillation, and cancer.^{27–29}

The presence of an infection POA or a HAI are independent risk factors for ND and poor functional outcome. To our knowledge, this is the first study that investigates the association between type of infection and ND, and short-term outcome after stroke.^{27,30,31}

Patients with HAI were at greater odds of ND than patients who presented with an infection POA, regardless of infection etiology. Once other predictors for ND were adjusted for, infection POA was no longer associated with ND, but HAI remained significantly associated. These results support the idea that developing an infection is significantly worse for outcome prognosis than having an infection at the time of stroke admission. We postulate that this may be because of the brief period of immunosuppression observed in patients after stroke,³⁰ the differential genetic expression of virulence factors between HAI and community-acquired pathogens,³¹ the higher rates of antimicrobial resistance in HAI,³² or the fact that some patients may already be colonized with certain microbes and do not show symptoms because these microbes represent longstanding nonvirulent flora.^{33,34}

Our results also support the concept that HAI are a driving force behind the significance of infections as a predictor for ND and poor functional outcome. The non-significant association between infection POA and the outcomes of interest further support this concept. Preventing HAIs has the potential to reduce preventable harm to the patient and improve outcomes, particularly in patients who may be more susceptible to infection. We therefore encourage stroke care providers to identify patients at greater risk of HAI such as the elderly, patients presenting with severe strokes, patients requiring intubation or catheterization, or patients with comorbidities that predispose to infection to make concerted efforts to rigorously monitor these patients for the development of any HAIs. Although current evidence does not support the use of antibiotic therapy in acute stroke patients who do not show signs of infection,³⁵ further investigation is needed to assess if patients at greatest risk of infection as identified through validated tools^{36,37} may show functional and neurologic benefit from prophylactic antibiotic therapy.

Our study is unique in that it compares the clinical impact of infections POA with those acquired in the hospital, but it is not without limitations. Our study is exploratory and hypothesis generating. Our small sample size and retrospective data from a single institution limit its generalizability. Furthermore, our ability to detect differences in groups was limited by sample size. It is likely that the phenomenon of infection on admission is underestimated

by the study design chosen here, justifying future prospective studies. The exclusion of in-hospital strokes could have eliminated patients who had HAI and provided more insight into outcomes after stroke in patients with HAI before stroke onset. This study includes only short-term outcomes, as we were not able to follow patients after discharge, preventing us from assessing the long-term consequences of HAI among patients with ischemic stroke. Although long-term functional outcome cannot be evaluated directly, disability status at discharge has been shown to be a significant predictor of functional outcome at 90 days.³⁸ An additional limitation is how discharge disposition was classified. We classified discharge disposition as being good if a patient was discharged home or to inpatient rehabilitation. A patient's discharge destination may be affected by their insurance, clinical status, and underlying conditions; furthermore, not all patients discharged home do well. Despite its limitations, our study was able to assess the clinical impact of infections on arrival compared with those acquired in the hospital and evaluate how ND mediated the effect of infection on functional outcomes.

Conclusion

In our population, HAI represented a clinically significant adverse event faced by a large proportion of patients admitted for ischemic stroke. Our results showcase the importance of monitoring patients for HAI to prevent ND and subsequent poor functional outcomes. Despite the precautions taken at medical centers at preventing HAI, we still have much room for improvement. Optimization of medical management may eventually necessitate prophylactic treatment with antibiotics in patients at greatest risk of HAI if we intend to reduce the probability of ND and subsequent functional disability after stroke.

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Figure 1.

(A) Crude association between timing of infection and neurologic deterioration. (B) Adjusted association between timing of infection and neurologic deterioration. (C) Crude association between timing of infection and poor functional outcome. (D) Adjusted association between timing of infection and poor functional outcome. Abbreviations: HAI, hospital-acquired infection; POA, present on admission. The diamond symbol signifies the odds ratio with the bands extending from it the 95% confidence intervals.

Table 1

Baseline demographic information

Variable	Infection POA (N = 23)	HAI (N = 54)	No infection (N = 256)	P*	P†
Age, y, median (range)	76 (44–92)	73.5 (19–95)	63 (22–97)	.2978	<.0001
Gender, female, n (%)	11 (47.8)	21 (38.9)	111 (43.4)	.4664	.7393
Race, n (%)				.6716	.8806
White	6 (26.1)	16 (29.6)	74 (29.1)		
Black	17 (73.9)	35 (64.8)	169 (66.5)		
Hispanic	0	2 (3.7)	7 (2.8)		
Other	0	1 (1.8)	4 (1.6)		
Medical history, n (%)					
Stroke	10 (43.5)	19 (35.2)	105 (41)	.4918	.6914
Coronary artery disease	8 (34.8)	14 (25.9)	41 (16.1)	.4311	.0329
Atrial fibrillation	1 (4.8)	11 (20.4)	24 (9.5)	.0769	.0432
Diabetes	5 (21.7)	24 (44.4)	78 (30.7)	.0598	.0778
Hypertension	21 (91.3)	43 (79.6)	188 (74.3)	.1318	.1529
Dyslipidemia	9 (40.9)	21 (38.9)	111 (44.1)	.8702	.7693
Cancer	6 (26.1)	5 (9.3)	20 (7.8)	.0534	.0154
Active smoker	4 (17.4)	10 (18.9)	80 (32)	.2512	.0723
Smoker in last year	4 (17.4)	11 (20.8)	85 (34.3)	.2376	.0538
Delay from LSN to ED arrival, min, median (range)	197 (36–1190)	106 (23–1419)	228 (10–1372)	.2006	.1333
TOAST, n (%)				.1775	.0707
Cardioembolic	5 (21.7)	21 (38.9)	71 (27.7)		
Large vessel	5 (21.7)	14 (25.9)	63 (24.6)		
Small vessel	3 (13)	8 (14.8)	55 (21.5)		
> 1 cause	5 (21.7)	8 (14.8)	50 (19.5)		
No cause	3 (13)	1 (1.8)	5 (2.0)		
Other	2 (8.8)	2 (3.7)	12 (4.7)		
Cortical, n (%)	19 (82.6)	39 (78)	128 (57.7)	.2274	.0034
Admission NIHSS, median (range)	17 (0–34)	12 (1–26)	6 (0–29)	.2628	<.0001
Glucose median mg/dL (range)	121 (88–663)	137 (78–481)	113 (76–569)	.2146	.0221

Variable	Infection POA (N = 23)	HAI (N = 54)	No infection (N = 256)	P*	P†
IV tPA, n (%)	10 (43.5)	23 (42.6)	98 (38.6)	.9427	.7958

Abbreviations: ED, emergency department; HAI, hospital-acquired infection; LSN, last seen normal; NIHSS, National Institutes of Health Stroke Scale; POA, present on admission; TOAST, Trial of Org 10172 in Acute Stroke Treatment; tPA, tissue plasminogen activator.

* This P value is assessing the comparison between infection POA and HAI.

† This P value is assessing the 3-group comparison.

Table 2

Infection-specific associations with outcomes

Variable	Crude model			Adjusted model*		
	OR	95% CI	P	OR	95% CI	P
Neurologic deterioration						
Any						
UTI	4.6	2.4–8.8	<.0001	3.3	1.7–6.4	.0005
PNA	14.6	4.9–43.2	<.0001	10.1	3.3–30.6	<.0001
Bacteremia	4.4	1.6–11.9	.0036	3.3	1.1–9.7	.0298
POA						
UTI	3.9	1.4–10.9	.0094	2.3	.78–6.9	.1284
PNA	3.8	.85–17.8	.0805	2.1	.39–11.0	.3861
Bacteremia	2.8	.56–14.3	.2093	1.5	.25–8.6	.6619
HAI						
UTI	6.3	2.8–14.2	<.0001	4.6	2.0–10.7	.0003
PNA	49.9	6.6–376.5	.0002	34.4	4.5–263.1	.0007
Bacteremia	6.9	1.9–25.8	.0038	6.1	1.5–25	.0128
Poor functional outcome						
Any						
UTI	10.5	3.7–29.9	<.0001	6.3	2.0–19.5	.0016
PNA	23.4	3.2–174.5	.0021	12.7	1.4–116.7	.0247
Bacteremia	4.1	1.2–14.3	.0278	3.5	.68–17.6	.1335
POA						
UTI	4.4	1.2–15.7	.0239	1.5	.31–7.2	.6115
PNA	5.8	.69–49	.1037	2.5	.07–93	.6150
Bacteremia	3.8	.42–34.7	.2330	0.26	.009–7.9	.4471
HAI						
UTI [†]	n/a	n/a	n/a	n/a	n/a	n/a
PNA [†]	n/a	n/a	n/a	n/a	n/a	n/a
Bacteremia	9.3	1.2–71.9	.0338	15.9	1.4–183.9	.0270

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Abbreviations: CI, confidence interval; HAI, hospital-acquired infection; n/a, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PNA, pneumonia; POA, present on admission; tPA, tissue plasminogen activator; UTI, urinary tract infection.

* The adjusted model is adjusted for age, NIHSS at baseline, glucose on admission, and treatment with IV tPA.

[†] These values are not available because of issues with model convergence and low numbers.